QUINAZOLINE DERIVATIVES AS MEDICAMENTS

Field of the Invention

The invention relates to treating various disorders associated with enhanced activity of kinase p38-α and/or transforming growth factor beta (TGF-β). More specifically, it concerns compounds that are related to quinazoline as useful in these methods.

Background Art

A large number of chronic and acute conditions have been recognized to be associated with perturbation of the inflammatory response. A large number of cytokines participate in this response, including IL-1, IL-6, IL-8 and TNF. It appears that the activity of these cytokines in the regulation of inflammation rely at least in part on the activation of an enzyme on the cell signaling pathway, a member of the MAP kinase family generally known as p38 and alternatively known as CSBP and RK. This kinase is activated by dual phosphorylation after stimulation by physiochemical stress, treatment with lipopolysaccharides or with proinflammatory cytokines such as IL-1 and TNF. Therefore, inhibitors of the kinase activity of p38 are useful antiinflammatory agents.

Transforming growth factor-beta (TGF-β) denotes a family of proteins, TGF-β1, TGF-β2, and TGF-β3, which are pleiotropic modulators of cell growth and differentiation, embryonic and bone development, extracellular matrix formation, hematopoiesis, immune and inflammatory responses (Roberts and Sporn Handbook of Experimental Pharmacology (1990) 95:419-58; Massague *et al. Ann Rev Cell Biol* (1990) 6:597-646). Other members of this superfamily include activin, inhibin, bone morphogenic protein, and Mullerian inhibiting substance. TGF-β initiates an intracellular signaling pathway leading ultimately to the expression of genes that regulate the cell cycle, control proliferative responses, or relate to extracellular matrix proteins that mediate outside-in cell signaling, cell adhesion, migration and intercellular communication.